AWARD NUMBER: W81XWH-16-1-0741

TITLE: Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: An Intervention Study

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Boston, MA 02115

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE
Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: An Intervention Study

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0741

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Children's Hospital Corporation
Boston, MA 02115

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Neurodevelopmental (ND) disabilities, particularly executive function impairments, are currently the most prevalent, and arguably the most distressing, long-term morbidity in the burgeoning population with congenital heart disease (CHD). Deficits in executive function pose serious threats to the educational achievement and consequent future employability, insurability and quality of life of millions of children with CHD. These adverse sequelae carry profound clinical and financial implications. While accumulating evidence exists on the deficits of patients with CHD, research evaluating effective therapeutic strategies is notably absent. The Cogmed intervention has been shown to improve executive function in several pediatric populations, but has not been studied in the CHD population.

15. SUBJECT TERMS
None listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	17	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Each year, approximately 1 child in every 100 is born with Congenital Heart Disease (CHD), making it the most common birth defect. Neurodevelopmental disabilities, particularly executive function (EF) impairments, are currently the most prevalent, and arguably the most distressing, long-term morbidity in the population with CHD. Deficits in executive function pose serious threats to the educational achievement and future employability, insurability and quality of life of millions of children with CHD. The Cogmed Working Memory intervention has been shown to improve executive function in several pediatric populations, but has not been studied in the CHD population. This is the first randomized controlled trial to evaluate the efficacy of Cogmed in improving neurodevelopmental outcomes of children with critical CHD after infant open-heart surgery. Children who meet eligibility criteria and who agree to participate will be randomly assigned to an intervention or control group. Children in the intervention group will complete 25 35-40 minute sessions of Cogmed training for a duration of 5 weeks. Cogmed is a set of home-based, child-friendly, computerized activities that targets the active training of EF including visual and spatial working memory, attention and impulse control. The control group will receive the standard of care. Children in both groups will undergo a total of 3 neurodevelopmental assessments: 1) a baseline evaluation prior to group randomization, 2) a post-treatment evaluation (or a 5 to 7-week post-baseline evaluation for the control group) and 3) a 3 month-follow-up assessment after the cessation of the intervention (or around 4-5 months after the baseline for the control group). The latter assessment will indicate whether any gains in EF skills of the children in the intervention group are sustained after training. Parents and teachers will also complete questionnaires about children's EF, attention, and social behaviors to determine whether training affects behaviors of the intervention group at home and in school. The investigators will also identify the medical and surgical characteristics of children associated with intervention efficacy. This information will be helpful in targeting the intervention most efficiently in the future.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

-Congenital Heart Disease
-Neurodevelopmental Disorders
-School-aged Children
-Executive Function
-Working Memory
-Cognitive interventions
-Infant Open Heart Surgery
-Cogmed

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific aims:

1. To evaluate the immediate efficacy of home-based Cogmed Working Memory Intervention for neurodevelopmental outcomes including executive function, social development and ADHD symptom reduction in children with critical CHD after open-heart surgery.
2. To evaluate the longer-term effects of the Cogmed Working Memory Intervention at 3-month follow-up.
3. To explore cognitive, medical and socio-demographic factors associated with changes in neurodevelopmental and behavioral scores in children assigned to receive the intervention.

For the period Year 1, month 1-3, we had the following target milestones:

1) Submit protocol to the USAMRMC office and HRPO
2) Hire and train research staff (develop job descriptions for study coordinator, advertise, interview and hire the study coordinator, identify space for new staff.

→ *All milestones have been successfully 100% completed*

For the period report Year 1, months 4-6, we had the following target milestones:

1) Acquire all study materials including neurodevelopmental tests, licenses for Cogmed working memory intervention as well as initiate the order of iPads.
2) Complete staff training and finalize data report forms and REDCap protocol.
3) Obtain and review records of Cardiology Clinic to identify potentially eligible children.
4) Conduct a pilot training using the Cogmed Working Memory intervention with two healthy volunteers, ages 7-12 years old.
5) Initiate further eligibility screening by phone with potentially eligible families.
6) Initiate enrollment and complete first baseline assessment with randomization of the first participant to one of the trial arms (intervention or control).

→ *All milestones have been successfully 100% completed*

For the period report Year 1, months 7-9, we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention versus the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children on accessing and using the Cogmed Program.
3) Schedule and conduct the post-intervention evaluations (Visit 2) for the first time.
4) Monitor all participants' performances on Cogmed intervention.
5) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.

→ *All milestones have been successfully 100% completed*

For the period report Year 1, months10-12, we had the following target milestones:

1) Continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention versus the control group.
2) Continue visits to participants' homes to administer the iPad and instruct parents and children
3) on accessing and using the Cogmed Program.
4) Schedule and conduct the follow-up evaluations (Visit 3) for the first time.
5) Monitor all participants' performances on Cogmed intervention.
6) Hold bi-monthly research study meetings to discuss ongoing progress and milestones.

→ *All milestones have been successfully 100% completed*

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

All major activities for this annual report were successfully accomplished.
After local IRB approval, we submitted our protocol to the USAMRMC and received HRPO approval. We hired our study coordinator, Alison Lord, BA. She has undergone all Boston Children's Hospital training for new research personnel and has received training from Dr. Calderon. We identified space for all study personnel.

We acquired all research materials including neurodevelopmental tests and questionnaires as well as Cogmed licenses. We also obtained certification and acquisition of the NIH Toolbox Test of Neurological and Behavioral Function license. We purchased 20 iPads to administer the intervention. All research report forms were finalized and the REDCap protocol was successfully created and is currently being used for data entry.
We successfully completed a pilot training of Cogmed intervention with two healthy volunteer children (7-12 years old) and have confirmed the optimal conditions for the administration of the intervention for this age range.

We have continued the eligibility screening of cardiology clinic records. Currently, almost 50% of these records have been meticulously screened. Of those eligible from this initial screening, over 250 of them have received mail-packets detailing information from the study. The study coordinator, Alison Lord, BS, continues to collaborate with Drs. Newburger, Calderon, and Bellinger as well as the cardiology research nurse to screen for potential children eligible for our study. All of those who have received packets are contacted by the study coordinator, who conducts a phone screening in order to confirm all eligibility criteria.

Enrollment of eligible patients has continued. At this time we have enrolled 24 patients into the study with 10 more visits scheduled in the next few weeks and several more scheduled over the fall/winter. Those randomized to the intervention have had home visits in which they are instructed on using the iPad and Cogmed program. These patients are continuously monitored on their Cogmed performances.
We have also completed post-intervention (second visit) testing with 19 of our enrolled patients and 7 patients have completed follow-up testing (third visit) as well.

We do not have any results or outcomes at this point, because we will need to await enrollment completion. No adverse events have occurred during this period.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

In the next reporting period (Year 2 months 1-3 of the study), we will continue the eligibility screening as well as the enrollment, baseline assessments and randomization of children to the intervention *versus* the control group. We will also continue the visits to participants' homes to set up the iPad and instruct parents and children on accessing and using the Cogmed program. We will continue to conduct post-intervention (visit 2) and follow-up (visits 3) visits as well.

We will monitor all participants' performances on Cogmed intervention as well as continue to have bi-monthly research study meetings to discuss ongoing progress and milestones.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The identification and treatment of neurodevelopmental morbidity constitute a primary aim in medical care and a public health priority as the number of individuals with CHD soars. The proposed innovative study bridges important bodies of research in the fields of neuropsychology and CHD, representing the first RCT to evaluate the efficacy of remediation strategies for children with CHD. If proven effective, this type of neurocognitive intervention could be implemented in a clinical outpatient practice.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Currently, there is a large population of patients with long-term neurodevelopmental dysfunction that negatively impact their quality of life. Deficits in executive function, in particular, pose serious threats to their educational achievement and consequent future employability, insurability and quality of life. The results of this study are likely to improve clinical and public knowledge about the available preventive and/or treatment strategies for youth with CHD. This, in turn, may positively affect policies regarding the clinical implementation of evidence-based interventions in this population which will likely have a significant economic and social impact.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

In the most recent quarter, we have experienced a slower pace of enrollment of new participants. We think that this may be due to the beginning of the new school year, when families are generally less available. In order to increase our enrollment rates in the next quarter, packets were sent out to additional families and we placed brochures on additional clinic offices. Thanks to these strategies, we have seeing a substantial increase in participation, with ten more baseline visits scheduled in the following weeks. Additionally, we will seek IRB/DoD approval to advertise on parent advocacy sites, as well as to expand recruitment to sites at greater distance from Boston Children's Hospital. Finally, if these steps do not increase the rate of enrollment, we have flexibility to extend enrollment from the current plan of Month 6, Year 2, to Month 1, Year 3, which will still give us 6 full months for final data analyses.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal;*

volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

clinicaltrials.gov
This website is a NIH online database of private and public clinical studies. Currently only a description of the study and contact information are displayed as there are no findings yet.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name: Jane Newburger, MD, MPH
Project Role: Principal investigator
Research Identifier ORCID number: 0000-0002-7794-9017
Nearest person month worked: 1.2 calendar months
Contribution to Project: Dr. Newburger (PI) has assured the coordination and supervision of this study. She has reviewed patient enrollment criteria, ensured data quality forms and maintained effective communication with study investigators.

Name: Johanna Calderon, PhD
Project Role: Co-Investigator
Research Identifier ORCID ID: 0000-0002-2644-6858
Nearest person month worked: 7.8 calendar months
Contribution to Project: Dr. Calderon has coordinated all aspects of the IRB submission and approval. She has prepared the protocol and has taken responsibility for the hiring and training of neurodevelopmental specialists and the study coordinators. She has prepared the case-report and REDcap forms as well as the randomization strategy in consultation with the team's biostatisticians. Dr. Calderon has conducted most of the neuropsychological assessments and co-directs the neurodevelopmental scientific aspects of the project.

Name: David C. Bellinger, PhD
Project Role: Co-Investigator
Research Identifier ORCID number: 0000-0003-3393-0119
Nearest person month worked: 4.8 calendar months
Dr. Bellinger has participated in study preparation. He has participated in the logistic preparation of staff training as well as in the neurodevelopmental aspects of the trial. He has supervised the research coordinators. Dr. Bellinger has conducted neurodevelopmental evaluations and provides scientific advice to the team for all aspects of the project.

Name: David Wypij, PhD
Project Role: Co-Investigator
Research Identifier ORCID number: 0000-0001-8367-8711
Nearest person month worked: 1. 8 calendar months
Dr. Wypij has served as this trial's senior biostatistician. He has supervised all aspects of study design, protocol development, database management, data entry and quality control. He has supervised the development of form design, data base structure and procedures and has oversight a Master's Level biostatistician, Christian Stopp.

Name: Christian Stopp, MS
Project Role: Biostatistician
Research Identifier ORCID number: 0000-0002-6360-5993
Nearest person month worked: 2.4 calendar months
Mr. Stopp has been responsible for formatting, programing needs and has developed the REDCap forms, in collaboration with Drs. Wypij and Calderon.

Name: Alison Lord, BS
Project Role: Study Coordinator
Research Identifier ORCID number: 0000-0003-2275-878X
Nearest person month worked: 12 months
Ms. Lord has undergone neurodevelopmental testing and Cogmed Working Memory Training in order to administer the intervention to children with CHD. She has participated in the logistic organization of this study. In collaboration with Dr. Newburger, Carolyn Dunbar Masterson, RN, and Donna Donati, she performs the medical record screening of potentially eligible patients as well as enrolling and consenting those found to be eligible. She then provides patients and their parents an iPad and training necessary to complete the intervention.

Name: Donna Donati
Project Role: Senior Study Coordinator
Research Identifier ORCID number: 0000-0001-7435-4504
Nearest person month worked: .12 calendar months
Ms. Donati has participated in the logistic organization of this study (hiring and training of Ms. Lord).

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable;

however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.